Chapter 4. Developmental Toxicity: II. Postnatal Manifestations

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and postnatal development, and ETS exposure and sudden infant death syndrome (SIDS), from the 1997 OEHHA report and from this update is provided below in Table 4.0. The findings are based on a weight of evidence approach.

Table 4.0 ETS, SIDS, Postnatal Development: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Findings: OEHHA 1997 Evidence of causal association?	Findings: Update Evidence of causal association?
SIDS	10	9	Conclusive	Conclusive (strengthened)
Cognition and Behavior	11	3	Suggestive	Suggestive
Postnatal physical development[a]	5	0	Inconclusive	Unchanged
CNS changes[b]	0	2	Not assessed	Suggestive (animal model)
Cardiovascular[c] Hematological Immune	0	6	Not assessed	Suggestive

[a] Measured as height gain [b] Includes changes in brain structure and receptor numbers.
[c] Includes changes in cardiac receptor numbers, HDL-C, RBC type and count, and allergic sensitization.

In summary, ETS exposure has been shown to cause SIDS. The available evidence suggests an association between ETS exposure and postnatal cognitive and behavioral, immunological, hematological, and cardiovascular effects.

4.0. Introduction

In the 1997 OEHHA report (Cal/EPA, 1997), passive and active maternal tobacco smoke exposure, as well as passive smoke exposure in children, were seen to have a deleterious effect on specific childhood outcomes. These included postnatal development, cognition and behavior, and the incidence of SIDS. This chapter examines the research in these areas published since that review. The chapter is subdivided into sections on SIDS and on other developmental effects of passive smoke exposure. In the studies included here, a child's exposure to ETS generally represents a continuation of the passive exposure it received *in utero* from maternal prenatal smoking. For this reason it is often not possible to ascribe specific outcomes exclusively to

exposures from one versus the other route. Indeed it appears that the prenatal smoke exposure a fetus may or may not receive partly determines its response to subsequent ETS exposure as an infant. The situation is complicated further by the consistent association of smoke exposure with other risk factors for negative childhood outcomes. Thus appropriate study design and control for these confounding factors are critical to the delineation of the role of ETS. While the emphasis in these studies is on the child's passive exposure to smoke, studies that specifically examined the childhood consequences of a mother's passive exposure to ETS during pregnancy included persistent pulmonary hypertension in infants (Bearer *et al.,* 1997) and fetal hypoxia (Dollberg *et al.,* 2000).

4.1. Sudden Infant Death Syndrome (SIDS)

This review utilizes the following definition of SIDS from the previous document:

> "Sudden Infant Death Syndrome (SIDS) is generally defined as the sudden death of any infant which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death (Beckwith 1970). The diagnosis of SIDS is usually restricted to infants aged one month to one year, but investigators sometimes expand the age-at-death criterion. In the United States and other developed countries, SIDS is the most common cause of post-neonatal death. Maternal risk factors that have been identified include young age, high parity, low socioeconomic status, cigarette smoking and illicit drug use; risk factors in the infant include male sex, black or American Indian race, prematurity, low birth weight, a history of recent illness, having a "near-miss SIDS episode", having a sibling who died of SIDS, not breast feeding, and sleeping in the prone position; other risk factors include the winter season (Kraus & Bulterys 1991; Guntheroth & Spiers 1992).

The 1997 OEHHA report reviewed 10 epidemiological studies that examined the relationship between ETS exposure and SIDS. Although these studies vary in quality and size, they all support an association between passive smoke exposure and SIDS. In that review was the following assertion:

> "In conclusion, the strength of the (Klonoff-Cohen *et al.*, 1995 and Blair *et al.*, 1996) studies, their consistency with two earlier well-conducted studies (Mitchell *et al.*, 1993

and Schoendorf & Kiely, 1992), and the identification of dose-response relationships provide sufficient evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS.

The studies published since that time generally reflect a heightened appreciation and control for various confounding factors while continuing to support this conclusion. While the difficulties associated with distinguishing the effects of pre- versus postnatal smoke exposure remain, demonstration of elevated cotinine and/or nicotine levels in SIDS victims compared to controls clearly supports a postnatal effect of ETS on SIDS (Milerad *et al*., 1998; Rajs *et al*., 1997; (McMartin *et al.*, 2002). Described below are six studies in humans and two reviews published since the 1997 Cal EPA report that support an association of passive smoke exposure and SIDS. Animal studies include the study by Slotkin *et al*. (1999) in rats suggesting a mechanism by which passive smoke exposure may increase the risk of SIDS by altering the development of the heart and brain. Altered brain development was also observed by Gospe *et al*. (1996) in rats exposed to side stream smoke. In piglets, Froen *et al*. (2000) found evidence implicating nicotine in combination with infection as a cause of SIDS. These effects may be exacerbated by the higher levels of fetal hemoglobin (HbF) in neonates that are associated with prenatal smoke exposure (Fagan *et al.*, 1995) and tighter binding of CO, and with increased incidence of SIDS (Giulian *et al.*, 1987; Gilbert-Barness *et al.*, 1993; Cochran-Black *et al.*, 2001).

4.1.1. Newer Epidemiologic Data

Table 4.1 ETS and SIDS

Reference Country	Study Description	Exposure to smoke	Outcome and OR (95% CI)	Comments
Milerad *et al*. 1998 Scandinavia	Case-control: cotinine in peri-cardial fluid in victims of sudden death. n = 45	Post +/- prenatal . SIDS Accidental Infection	Cotinine (ng/ml) Median (range) 15.8 (3.5-110) 12.9 (2.1-114) 7.1 (1.2-15.4)	Cotinine reflected recent nicotine exposure prior to death in infants: 24 SIDS, 12 infection, 9 accidents No ETS: 0-0.4 ng/ml; when both parents smoke: 2.4-5.4 ng/ml
Rajs *et al*. 1997 Sweden	Cohort: cotinine and nicotine in pericardial fluid in victims of SIDS and non-SIDS death. n = 85	Postnatal +/- prenatal	SIDS assoc with cotinine > 30 ng/ml. In SIDS nicotine incr. with age.	Pericardial fluid taken at autopsy fr 50 male, 35 female SIDS (67) and non-SIDS (18) infants. Suggests SIDS assoc. with elevated cotinine or nicotine.

Table 4.1 ETS and SIDS (cont.)

Reference Country	Study Description	Exposure to smoke	Outcome and OR (95% CI)	Comments
McMartin *et al*. 2002 Canada, US	Case-control Measured cotinine and nicotine in lungs from victims of SIDS and non-SIDS death. n = 73	Postnatal SIDS Non-SIDS Smoking Non-smoking Smoking Non-smoking	Nicotine (ng/g) 19.64 ± 2.61 7.86 ± 1.63 (p=0.0001) 19.92 ± 2.63 7.86 ± 1.68 (p=0.0001) Cotinine (ng/g) 13.48 ± 2.41 5.04 ± 0.57 (p=0.0001)	Lungs from 44 SIDS and 29 non-SIDS victims for nicotine and cotinine measurements. Data stratified by household smoking status, also by SIDS vs non-SIDS. Study can't definitively distinguish pre- vs postnatal passive exposure due to possible reporting bias. Nicotine in lungs supports ETS exposure prior to death.
Alm *et al*. 1998 Scandinavia	Case-control: smoke exposure in SIDS victims. n = 218	Maternal Prenatal only Ceased while pregnant Pre+postnatal	SIDS OR 1.1 (0.5; 2.4) 1.1 (0.4; 3.2) 4.5 (3.1; 6.5)	Assessed smoking habits before, during and after pregnancy by questionnaire in families of SIDS victims. If smoking stopped at delivery, risk of SIDS dropped suggesting postnatal ETS effect.
Mitchell *et al*. 1997 New Zealand	Prospective case-cohort of risk factors for SIDS n = 1,049	Maternal 1-19 cig/d > 20 cig/d Postnatal Maternal Shared bed Paternal	SIDS OR unadj: 5.84 (3.72-9.21) 14.89 (6.38-34.72) SIDS OR adj: 1.43 (0.58-3.51) 5.02 (1.05-24.05) 3.84 (2.49-5.92)	SIDS risk increased with more post-natal maternal smoking. No control for prenatal smoking. Increased risk with paternal smoking or bed sharing with smoking mother supports post-natal ETS effect.
Brooke *et al*. 1997 Scotland	Case-control of infant care practices and SIDS. n = 577	Smoking Both parents Mom only Dad only	SIDS OR adj 5.19 (2.26-11.91) 5.05 (1.85-13.77) 2.12 (0.99- 4.56)	201 SIDS in 798 postnatal deaths. Good confounder control. Risks if both parents or father only smoked suggest postnatal ETS effect. Dose response (p = 0.001).
Anderson & Cook 1997	Meta-analysis of studies on pre- and postnatal smoking SIDS	Maternal Postnatal	SIDS OR adj 1.94 (1.55-2.43)	5 of 8 studies that examined postnatal smoking and controlled for prenatal smoking found increased SIDS with postnatal ETS exposure.
Dwyer *et al*. 1999 Tasmania	Prospective cohort of ETS and SIDS at 1 mo. n = 9,826	Mom post 1-10 cig/d 11-20 > 20	SIDS OR adj 2.08 (0.79-5.48) 2.15 (0.85-5.47) 4.69 (1.74-12.58)	Good correlation of postnatal ETS and SIDS but not with cotinine. Postnatal effect may be continuation of prenatal maternal smoking.
Elliot *et al*. 1998 Australia	Case-control Compared airways of SIDS victims with vs without smoke expo. n = 36	Maternal > 20 cig/d No smoke	Inner wall area/Pbm 0.07 ± 0.013 0.055 ±0.008	Smoke exposure increased thickness of inner wall ($p<0.05$) and epithelium ($p< 0.01$) of large airways. Can't separate pre- vs postnatal exposure.

Milerad et al., 1998. This study compared levels of cotinine in pericardial fluid from all cases of sudden death of children in southeastern Norway during 1990-1993. Included were 24 infants who died of SIDS, 12 who died from infections and were matched for age and sex with the SIDS cases, and 9 who died from accidents. Cotinine was used as an objective measure of recent nicotine exposure. Due to the rate of metabolic conversion of nicotine to cotinine and the fact that nicotine metabolism ceases after circulatory arrest, cotinine levels in pericardial fluid obtained at autopsy were taken to reflect nicotine exposure 4-8 hrs before death. In this study pericardial cotinine levels >5 ng/ml were used to identify infants significantly exposed to nicotine shortly prior to death.

The median and range of cotinine concentrations for SIDS infants was 15.8 (3.5-110) ng/ml. This was significantly higher than the 7.1 (1.2-15.4) ng/ml for the deaths by infection ($p<0.003$) but not significantly different from the levels found in the accidental deaths (12.9; 2.1-114 ng/ml). Of the SIDS victims, 92% (22/24) had cotinine levels exceeding 5 ng/ml of which 6 (25%) had levels > 20 ng/ml. Among the infants who died of infection, 67% (8/12) had cotinine levels above 5 ng/ml and none above 20 ng/ml. In the 9 accident victims, 78% had cotinine levels above 5 ng/ml and 33% were above 20 ng/ml. Since smokers have a significantly increased risk of being involved in automotive accidents (Brison,1990), children of smoking parents may be over-represented in traffic accident fatalities. In addition, exposure to ETS in the car prior to the accident would increase pericardial nicotine.

Based on the objective measure of cotinine in a body fluid, this study strongly supports a connection between an infant's recent exposure to ETS and SIDS. It is not clear to what extent prenatal exposures to tobacco smoke may have contributed to the infant's susceptibility to SIDS, however the high levels of cotinine in the SIDS victims are consistent with intense ETS exposure as a precipitating event.

Rajs et al., 1997. Pericardial fluid was collected at autopsy from 85 infants (50 male, 35 female) under the age of 1 year who died from SIDS (n=67) and non-SIDS (n=18) causes. Infant exposure to tobacco smoke was investigated by questionnaire in 18 cases (61% of the questionnaires sent out). The data collected included prenatal exposure, number of cigarettes smoked per day, smoking in infant's presence, and breastfeeding. Whereas in non-SIDS infants

pericardial nicotine decreased with increasing age (p=0.014), in SIDS victims there was a tendency towards increasing nicotine with increasing age (p=0.071). While cotinine levels appeared not to change with age in both groups, for victims under 4 months of age, all infants with cotinine concentrations exceeding 30 ng/ml in the pericardium died of SIDS. Otitis media was noted in 12 of 85 deaths with the highest incidence (33.5%) in infants with high nicotine levels in the pericardium. The incidence of cardiovascular alterations (of unspecified nature) reportedly increased with increasing nicotine and cotinine levels. Foci of mononuclear leukocytes in the pancreas were associated with high cotinine levels (p=0.012). Pathological findings in the upper and lower respiratory tract were associated with intermediate levels of cotinine perhaps indicating that the alterations developed after the metabolism of nicotine to cotinine. There thus appeared to be an association between SIDS and levels of nicotine and cotinine in the infant.

This was a small study and the response rate to questionnaires smaller still. Control for other potential contributors to SIDS, such as prenatal alcohol and drug use, presence of infectious agents, diet, etc. was not uniform across subjects. There was likely bias in the smoke exposure data as the highest nicotine and cotinine levels were found in infants whose parents failed to return the questionnaires. Since there was no control for mother's prenatal smoke exposure, it is not possible to separate postnatal effects of ETS from prenatal exposure which may have predisposed the infant to SIDS. However the correlation between SIDS and high current nicotine and cotinine implicates postnatal ETS exposure in elevated SIDS risk.

McMartin et al., 2002. Nicotine and cotinine levels were measured in the lungs of 44 SIDS and 29 non-SIDS victims with the results stratified according to reported household smoking status. Significantly higher nicotine levels were found in SIDS cases (19.64 ± 2.61 ng/g) compared to non-SIDS cases (7.86 ± 1.63 ng/g)(p=0.0001) irrespective of reported smoking status. Cotinine levels, however, were not significantly different between these two groups (10.87 ± 2.32 vs 8.71 ± 1.47 ng/g)(p=0.2). When all cases were compared, nicotine and cotinine levels were significantly higher in infants from identified smoking vs nonsmoking households: nicotine 19.92 ± 2.63 vs 7.86 ± 1.68 ng/g (p=0.0001); cotinine 13.48 ± 2.41 vs 5.04 ± 0.57 ng/g (p=0.0001). Probable bias in the reporting of smoking history limits this study's ability to correlate SIDS with prenatal vs postnatal smoking. Nevertheless, elevated nicotine levels in the lungs of SIDS vs non-SIDS victims strongly indicates an involvement of postnatal ETS in SIDS.

Alm et al., 1998. This case-control study in Scandinavia used postal questionnaires to examine the association between maternal and paternal smoking habits before, during and after pregnancy in 218 families of SIDS victims. Cases and controls were matched for gender but controls were slightly older (21.4 vs 16.1 wks). Odds ratios were adjusted for maternal and infant ages, and birth weight. SIDS risk was elevated with maternal smoking before (OR 2.5, 95% CI 1.7; 3.7), during (3.6, CI 2.4; 5.3), and after (3.7, CI 2.5; 5.5) pregnancy. The effects of smoking cessation and its timing were also examined and crude ORs reported for the comparison with never smokers. If smoking stopped prior to pregnancy the OR was 0.7 (95% CI 0.3; 1.4). Cessation at parturition gave an OR of 1.1 (0.5; 2.4) while cessation during pregnancy with resumption after birth gave OR 1.1 (0.4; 3.2). This compares to an OR of 4.5 (3.1; 6.5) for continuous maternal smoking during pregnancy and after. The drop in the risk for SIDS when the mother stopped smoking at parturition compared to that for continued smoking suggests that postnatal ETS is associated with SIDS. This effect may be partially due to other changes in maternal behavior of which smoking cessation was a part. The low risk seen if the mother stopped only during pregnancy supports the importance of prenatal exposure and is consistent with postnatal ETS being more deleterious if the infant was also exposed prenatally. If mothers who stopped smoking during pregnancy and resumed smoking postnatally are more likely to not smoke around their children, then the additive effect of prenatal to postnatal smoking may be overstated.

Mitchell et al., 1997. This was a prospective case-cohort study to identify risk factors for SIDS following a national campaign to prevent SIDS. Data from all SIDS cases plus a random sampling of control infants from births occurring between 10/1/1991 and 9/30/1993 in New Zealand were used with a case-control methodology. During the initial interview, and again when the infants were two months of age, data were collected on such variables as parental smoking during the previous 24 hrs, type of infant feeding, infant sleeping position and whether infant slept with the mother. Additional information obtained in the initial interview included infant's gender, birth weight, and gestation length, as well as maternal age, marital status, education, ethnicity, parity, antenatal care, and smoking habits.

Maternal smoking during pregnancy was associated with elevated incidence of SIDS with an OR of 6.05 (95% CI 3.90;9.40). After birth, the risk of SIDS increased with increasing levels of maternal smoking in the previous 24 hrs. At the initial interview, when mother and child did not

share the bed, the SIDS risk associated with postnatal maternal smoking of 1-19 cigarettes/day had an unadjusted OR of 5.84 (95% CI 3.72;9.21) that increased to 14.89 (6.38;34.72) with 20 or more cigarettes. At the two-month visit, these ORs were 4.90 (95% CI 2.65;9.06) and 21.42 (95% CI 6.89;66.52), respectively. After adjusting for maternal age, marital status, age mother left school, parity, infant gender, ethnicity, birth weight, sleep position and breastfeeding, the OR for SIDS associated with maternal smoking at two months of age was 1.43 (95% CI 0.58;3.51) which increased to 5.02 (95% CI 1.05;24.05) with bed sharing (Table 4.2). The increased SIDS risk when a child shares the bed with a smoking mother may be due to more concentrated ETS exposure. By comparison, there was no significant increase in SIDS when a nonsmoking mother and child shared the bed (OR 1.03; 95% CI 0.21;3.51). Paternal smoking was also associated with an increased risk at both the first (OR 3.84; 95% CI 2.49;5.92) and second (OR 3.21; 95% CI 1.81;5.71) visits. These data support postnatal ETS exposure as a risk factor for SIDS independent of prenatal smoke exposure.

Table 4.2 Risk of SIDS with Maternal Postnatal Smoking and Bed-sharing

Bed-sharing/ Maternal smoking	SIDS OR adjusted (95% CI) 1st visit	SIDS OR adjusted (95% CI) 2 month visit
No/No	1.00	1.00
No/Yes	1.68 (0.84; 3.34	1.43 (0.58; 3.51)
Yes/No	0.55 (0.17; 1.78)	1.03 (0.21; 3.51)
Yes/Yes	5.01 (2.01; 12.46)	5.02 (1.05; 24.05)
Paternal smoking	3.84 (2.49; 5.92)	3.21 (1.81; 5.71)

Brooke et al. (1997) examined the relationship between infant care practices and the incidence of SIDS in Scotland from 1992 to 1995. Of the 798 post-perinatal deaths recorded with the Scottish registrar general, 201 were diagnosed as SIDS. Controls were matched for age, season of birth and maternity unit. Questionnaires were completed by the mothers during a home visit and provided core medical and social data as well as information on prenatal factors, feeding regimen, sleeping habits and environment, illnesses, and exposure to smoking. Odds ratios were calculated from both uni- and multivariate analyses, with the latter adjusted for a large number of factors including specifics of sleeping position and habits, gender, maternal age and education, birth weight, breast feeding, social class, parity, drug use, and parental smoking. Parental smoking was significantly associated with SIDS (p= 0.0001). If both parents smoked, the adjusted OR for SIDS was 5.19 (95% CI 2.26-11.91) while the OR for maternal only smoking

was 5.05 (95% CI 1.85-13.77). Paternal-only smoking had an OR of 2.12 (95% CI 0.99-4.56). A dose response was associated with increased smoking by the mother (p=0.0001), father (p=0.0001), and other household members (p=0.001). Due to the size of this study and the continuity of maternal smoking during and after pregnancy, it was not possible to distinguish the effects of pre- versus postnatal maternal smoke exposure. However, an effect of postnatal ETS is suggested by the OR of 2.12 for paternal only smoking.

Anderson & Cook (1997) conducted a meta-analysis of the effects of prenatal and postnatal smoke exposure on incidence of SIDS. Nine studies included data on postnatal maternal smoking of which four controlled for maternal prenatal smoking. The adjusted ORs for postnatal ETS exposure and SIDS from these studies were 1.75, 2.33, 1.79 and 2.28, with a pooled OR of 1.94 (95% CI 1.55-2.43). To more directly assess the effects of pre- versus postnatal ETS exposure, several studies examined the SIDS risks associated with other smokers in the household. The number of such studies was small and the results more variable so no meta-analysis was attempted. In a study by Mitchell *et al*. (1993), no effect of paternal smoking (OR 1.00) was found when the mother did not smoke, consistent with prenatal exposure making the infant more susceptible to subsequent ETS exposure. However, when the mother did smoke prenatally, an OR of 1.37 (95% CI 1.02; 1.84) was calculated for paternal postnatal smoking after adjusting for maternal smoking and other confounders. Similarly Blair *et al* (1996) found an OR of 2.50 (95% CI 1.5; 4.2) for paternal smoking after adjusting for maternal smoking and other confounders. In 5 of 8 reviewed studies for which smoke exposure *in utero* was controlled or excluded there appeared to be an increased risk of SIDS associated with postnatal ETS exposure independent of prenatal exposure.

Dwyer et al., 1999. This was a prospective study of ETS exposure at one month of age in relation to SIDS. The data were derived from the Tasmanian Infant Health Survey from 1988-1995, a prospective cohort study involving 9,826 infants assessed as being at high risk of SIDS. The analysis included 35 SIDS deaths. At the same time, a population-based retrospective case-control study was also conducted that provided retrospective data on SIDS cohort infants for whom prospective data were not available at 1 month of age. For the prospective study, initial interviews, conducted when the infants were 4 days old, collected data on maternal smoking habits during pregnancy, whether the mother lived with someone who smoked, number of

cigarettes smoked in the mother's presence per day inside and outside the house, and time spent in the same room with someone smoking. Infant and home environment measurements were taken during a home visit during the fifth postnatal week. At this time detailed information was collected on the number of cigarettes smoked per day, number of adult smokers in the house and whether the mother or others smoked in the same room as the infant. A follow-up interview was conducted when the infants were 12 weeks of age. Infant urinary cotinine levels were measured on samples collected during the home visits.

Maternal prenatal smoking was associated with reduced birth weight (p=0.0001) and reduced placental weight (p=0.02). After adjustment for prematurity, birth and placental weights, prenatal smoking was associated with an OR for SIDS of 2.76 (95% CI 1.18; 6.46). For postnatal exposure, univariate analysis gave an OR among infants in a home where the mother and others smoked of 2.83 (95% CI 1.09; 7.37) which was not higher than the OR of 4.48 (95% CI 1.65; 12.13) found in homes where only the mother smoked. It is not clear whether this unexpected result is related to the inclusion of women who smoked prenatally as well as postnatally. Smoking by other residents reportedly increased an infant's urinary cotinine by 63%, but did not appear to be related to SIDS incidence. After adjustment for socioeconomic variables (education, marital status, paternal employment, health insurance), and for such variables as season of birth, sleeping in a prone position, sex, low birth weight, bottle feeding, mother's age, delayed first immunization and family history of asthma, the OR for SIDS from maternal postnatal smoking was 3.44 (95% CI 1.49; 7.94). A dose response was suggested as the adjusted OR for maternal postnatal smoking of 1-10 cigarettes per day was 2.08 (95% CI 0.79; 5.48); 11-20 cigarettes per day, OR 2.15 (95% CI 0.85; 5.47); >20 cigarettes OR 4.69 (95% CI 1.74; 12.58). Retrospective but not prospective data on postnatal smoking were available for 14 of the infants who subsequently died of SIDS. Analysis of these data along with those from the retrospective case-control study reportedly gave similar estimates of risk from maternal and other resident's smoking. It gave an OR for postnatal smoking of 3.61 (95% CI 1.88; 6.93) and a significant trend for increased risk with increasing number of cigarettes smoked (p=0.047). Interestingly, overall there was no evidence of an increase in SIDS incidence associated with the presence of other smokers (adjusted OR 0.72; 95% CI 0.48; 1.46) even though there was an association between other smokers and urinary cotinine. However other smokers significantly raised the risk for SIDS

in households of older mothers (>19 yrs; OR 2.38; p=0.058) versus younger mothers (OR 0.32; p=0.0064). The reason for this effect is not clear.

Since maternal smoking habits tended not to change from before to after birth, the size of this study prevented clear separation of the effects of pre- versus postnatal smoke exposure. Nevertheless, these results were similar to the findings of the Tasmanian case-control study where maternal postnatal smoking was strongly associated with SIDS (OR 3.96; 95% CI 1.91; 8.24) but smoking by other household residents was not (OR 1.31; 95% CI 0.70; 2.44).

Elliot et al., 1998. This study asked whether the airways from infants who had died of SIDS and had been exposed to high levels of maternal smoking were structurally different from those who had died from SIDS and were not exposed. Data were collected by interview from mothers of SIDS infants on smoking history before, during and after pregnancy. During postmortem examination of transverse sections of lungs from SIDS victims, the perimeters of the internal epithelium, basement membrane, outer smooth muscle and outer airway were measured. This allowed estimation of the total, epithelial, inner and outer wall areas, and epithelial thickness.

Some 228 airways from 19 infants in the high-smoke exposure group (mother smoked >20 cigarettes per day) were compared with 158 airways from 19 infants with no exposure. To compare similar-sized airways from different subjects, airways were divided into three arbitrary size groups. The means of pooled measurements for each size group were compared between exposure groups. Inner wall areas were calculated by subtracting the area of a circle whose perimeter is that of the basement membrane from the area of a circle whose perimeter is that of the outer smooth muscle layer. For comparisons, the mean inner wall area (± SD) was expressed as a ratio to the basement membrane perimeter (Pbm). In the Pbm 2-4 mm group, this ratio was significantly greater in the smoke-exposed versus the unexposed infants (0.07 ± 0.013 vs 0.055 ± 0.008; $p<0.05$). The epithelial thickness in relation to Pbm was also significantly greater in the smoke-exposed group (0.03 ± 0.007 vs 0.02 ± 0.003; $p<0.01$). In the two smaller airway size groups (Pbm < 1 mm and Pbm 1-2 mm) there were no significant differences in the measured wall thicknesses. This study suggested that smoke exposure alters airway morphometry, increasing the wall thickness of the larger airways. Due to the small size of this study, it was not possible to assess the relationship between histologic changes and smoking history in the 45 cases

where the infants were exposed to varying levels of smoke. The authors thus restricted their analysis to the 38 cases where smoke levels were constant before, during and after pregnancy. This comprised 19 mothers with no smoke exposure and 19 who smoked >20 cigarettes per day for the duration. It was thus not possible to distinguish the effects of exposure *in utero* versus postnatal exposure to ETS nor to discern a possible dose response. It has been suggested that a direct toxic effect of postnatal ETS exposure on lung growth may occur secondary to altered lung growth from *in utero* exposure. This may predispose the infant to impaired lung function and increased risk of SIDS.

Thornton & Lee (1998) reviewed 28 prospective and case-control studies on the relationship between parental smoking and SIDS published from 1966 to 1996. Where available, adjusted and unadjusted relative risk values were extracted from the studies and the factors for which adjustment was made were indicated. An attempt was made to evaluate whether the risk attributed to smoke exposure was in fact attributable to other factors by analyzing the amount by which the risk values were changed after adjustment for confounders.

For maternal smoking during pregnancy, 28 of the 29 unadjusted risk values extracted were above 1.00, many significantly so. Moreover, the extracted adjusted values were also significantly above 1.00 indicating an effect of prenatal smoking on SIDS. However from four of the studies examined (Malloy *et al.*, 1988; Blair *et al.*, 1996; Mitchell *et al.*, 1993; Wierenga *et al.*, 1990) the adjustments reduced the relative risks of SIDS by as much as 59-80%. This was interpreted as indicating that a large portion of the excess risk of SIDS associated with maternal prenatal smoking may be due to other risk factors. Indeed, a large number of pre- and postnatal factors have been found to contribute to the risk of SIDS, many of which, such as lower socioeconomic and education levels, are also correlated with maternal smoking. Thus maternal smoking may well be a marker for some of these risk factors as well as a contributor in its own right.

Similar to the studies of maternal prenatal smoking, the nine studies reporting risks associated with postnatal maternal smoking reported unadjusted risk values significantly above 1.00 with variable and, in some cases, large reductions in risk estimates after adjustment (Table 4.3). This again reflects that multiple factors contribute to SIDS incidence.

Table 4.3 SIDS Risk and Maternal Postnatal Smoking

Study	Unadjusted RR	Adjusted RR	Adjustment factors
Bergman & Wiesner	2.42 (1.22; 4.82)	2.38 (1.17; 4.83) 2.05 (1.00; 4.24)	Maternal age Education
Blair et al	5.19 (3.57; 7.55)	--	--
Cameron & Williams	4.04 (2.63; 6.20)	--	--
Dwyer & Ponsonby	3.13 (1.06; 9.26)	Became non-sig.	Maternal age
Klonoff-Cohen et al Any Same room	 3.13 (1.75; 5.60) 6.17 (2.60; 14.61)	 2.28 (1.04; 4.98) 4.62 (1.82; 11.77)	Antenatal classes, breast feeding, birth weight, medical condition, maternal smoking prenatally, sleep position.
McGlashon	1.92 (1.26; 2.92)	--	--
Mitchell *et al.* Any In house Never in house	 4.24 (3.35; 5.36) 2.20 (1.38; 3.51) 5.07 (1.50; 15.41)	 1.79 (1.30; 2.48) -- --	Postnatal age, antenatal classes, breast feeding, bed sharing, birth weight, gestational age, neonatal intensive care, maternal age and age at first pregnancy, medical condition, months pregnant, pregnancy smoking, race, region, season, education, socio-economic status, sleep position, time of day.

Data from Thornton and Lee (1998).

Table 4.4 SIDS Risk and Paternal Smoking

Study	Unadjusted RR	Adjusted RR	Adjustment factors
Bergman & Wiesner	1.53 (0.78; 3.01)	-	-
Blair et al	3.04 (2.13; 4.36)	2.50 (1.48; 4.22)	Maternal alcohol use, breast feeding, bed sharing, birth weight, illegal drug use, gestational age, maternal age, marital status, parity, socioeconomic status, sleep position, type of birth.
Cameron & Williams	1.85 (1.32; 2.60)	-	-
Klonoff-Cohen et al During pregnancy After birth After birth in same room	 3.56 (2.11; 6.00) 3.53 (1.99; 6.27) 9.20 (3.66; 23.15)	 3.46 (1.91; 6.28) 8.49 (3.33; 21.63)	Antenatal classes, breast feeding, birth weight, medical condition, maternal smoking in pregnancy, sleep position.
Lewak et al	No association	-	-
McGlashon	1.73 (p = 0.05)	-	-
Mitchell et al	2.41 (1.92; 3.02)	1.37 (1.02; 1.84)	Postnatal age, breast feeding, birth weight, maternal age, marital status race, region, sex, socioeconomic status, sleep position, time of day.
Nicholl & O'Cathain	-	1.63 (1.11; 2.40)	Birth weight, maternal age, parity, state of major accommodation.

Data from Thornton and Lee (1998).

Smoking by the father or other partner was investigated in only eight studies (Table 4.4). Two of these studies reported either no or a non-significantly elevated association with SIDS. The rest of the studies reported a significant association including one by Klonoff-Cohen that reported a greater association of SIDS with paternal than with maternal smoking.

After recognizing the limitations of the studies, alternative interpretations and the possible confounding factors, the authors concluded that "for all the indices of exposure considered, there does appear to be evidence of an increase in SIDS risk in relation to an increase in the extent of exposure to tobacco smoke."

4.1.2. Animal Studies of SIDS and Tobacco Smoke Exposure

Slotkin et al., 1999. SIDS is thought to be evoked by episodes of hypoxia; the mammalian response to hypoxia is mediated by the autonomic system acting through cholinergic receptors. Rats were used to model the role of pre-and postnatal nicotine exposure on the expression of cholinergic receptors in neonatal brain and heart. Pregnant rats were implanted with osmotic minipumps to provide continuous delivery of buffer (controls) or nicotine bitartrate to give doses of 2 or 6 mg/kg/day, levels which approximate moderate and heavy smoking in humans. For experiments involving postnatal exposure, pups were given subcutaneous injections of nicotine or vehicle corresponding to 0.3 or 3 mg nicotine, twice daily for 4 days. These injections occurred on days 1-4, 11-14, or 21-24 with the animals necropsied on days 5, 15 or 25 and the hearts and brains removed for receptor determinations.

In cardiac tissue, acetylcholine decreases contraction rate via its activation of cardiac muscarinic type 2 receptors (M2) and the subsequent inhibition of adenylyl cyclase. In the heart, prenatal but not postnatal nicotine exposure at both doses caused a significant overall increase in M2 receptor numbers and binding at 18 days of age ($p<0.03$) as shown by receptor binding assays. Nicotine exposure has been shown previously to cause a decrease in ß-adrenergic receptors (Navarro *et al.,* 1990). These changes in receptor numbers altered cellular function as manifested in the ability of muscarinic and adrenergic agonists to modify adenylyl cyclase activity in cardiac membrane preparations. As would be expected from an increase in the inhibitory M2-receptors concomitant with a decrease in ß-adrenergic receptors, isoproterenol, a ß-adrenergic agonist, showed an

impaired stimulatory response with nicotine treatment while carbachol, a muscarinic receptor agonist, showed enhanced inhibition of adenylyl cyclase.

Prenatal nicotine exposure in the brainstem, in contrast to the heart, did not enhance M2 receptor numbers. Instead the entire pattern of receptor acquisition and loss was delayed so that deficits were seen early in postnatal development. Also, unlike the heart, administration of nicotine immediately after birth caused a deficit in brainstem M2 receptors similar to that seen with prenatal exposure that was significant at the higher dose (3 mg/kg/day; $p<0.02$). While nicotine decreased M2 receptors in the brainstem, both doses increased nicotine receptors on day 5 after 4 days of postnatal nicotine exposure. However, on days 11-14, this up regulation was seen only at the higher dose and was not seen with either dose after treatment on days 21-24. The authors suggest that these data indicate a late prenatal to early postnatal window of sensitivity to these effects of nicotine in rats, the timing of which is developmentally equivalent to the last trimester in humans.

The maintenance of cardiac function, and thus cerebral perfusion, are dependent on catecholamine release and on the transduction of the adrenergic signal via cardiac ß-receptors. In contrast, the inhibitory vagal innervation is competent earlier, can be activated by stress, and operates on the cardiac signaling pathway mediated by M2 receptors. Thus the reduction in the stimulatory ß-adrenergic receptors and the increase in inhibitory M2 receptors induced by nicotine exposure will impair cardiac performance during periods of hypoxic stress. In addition, the observation in this study of a nicotine-induced reduction in brainstem muscarinic receptors parallels that seen in infants who have died from SIDS. In these infants there was decreased binding in brainstem areas associated with cardiorespiratory functions (Kinney *et al.,* 1995). Thus via nicotine, ETS exposure may contribute to the risk of SIDS by impairing the ability of the brain and heart to respond appropriately to periods of hypoxia. The hypoxia in turn may be caused by elevated HbCO, also resulting from ETS exposure.

Froen et al., 2000. Insufficient autoresuscitation following apnea in infancy is associated with SIDS. In addition, at the time of death SIDS victims frequently have a slight infection and a stimulated immune system. Froen *et al*. exposed piglets to nicotine and/or interleukin-1ß (IL-1ß) to simulate the effects of ETS exposure with and without simultaneous infection on

autoresuscitation following induced apnea. IL-1ß was used as it is a prototypic inflammatory cytokine released in the inflammatory response accompanying an infection. In these experiments, intravenous administration of IL-1ß (10 pmol/kg) simulated IL-1ß release during infection. Nicotine exposure (5 µg/kg) was in the same range as that received by an infant exposed to ETS and breastfed by a smoking mother (0.1-6.5 µg/kg). In untreated animals, induction of apnea resulted in a drop in heart rate and blood pressure followed by autoresuscitation and a rapid increase in heart rate, blood pressure and respiration rate. Nicotine treatment resulted in more and repeated spontaneous apneas that prevented the compensatory increase in respiration rate following induced apnea. IL-1ß treatment caused prolonged apneas and an inability to hyperventilate. The effects of nicotine and IL-1ß combined were additive with more spontaneous and longer lasting apneas, loss of normal hyperventilation after induced apnea, and dramatically decreased respiration rates. This resulted in lowered arterial pH and pO_2, and elevated pCO_2 up to 5 minutes after induction of apnea. Thus, in this piglet model, nicotine exposure at levels obtainable in infants exposed to ETS and breast milk from a smoking mother interferes with normal autoresuscitation after apnea. This effect is significantly worsened in the presence of an underlying infection, both of which predispose to SIDS.

Gospe et al., 1996. This study in rats examined whether ETS exposure *in utero* and/or postnatally altered the biochemical composition of rat brains. Side stream smoke (SS) was used as surrogate for ETS and had a total suspended particulate concentration of 1.00 ± 0.07 mg/m^3, CO of 4.9 ± 0.7 ppm, and nicotine of 344 ± 85 µg/m^3. The CO concentrations were typical of smoky bars but the nicotine and particulate concentrations were 30 and 10 times higher, respectively. Four scenarios were designed which gave control (filtered air), prenatal only, postnatal only, and prenatal with postnatal exposures. Exposures were for 4 hr/d, 7 d/wk from day 3 of gestation until delivery for prenatal exposure, and from birth to 9 weeks of age for postnatal. At necropsy the brains were removed and divided into fore- and hindbrains. Levels of protein, DNA and cholesterol were assayed in the respective brain halves as indices of brain development.

Prenatal exposure to SS did not alter these three biochemical indices of brain development (protein, DNA and cholesterol levels) whereas postnatal exposure caused a decrease in DNA concentration. No interaction between pre- and postnatal exposures was detected so the data were pooled into two groups: animals with and without postnatal exposure. Postnatal exposure to SS

significantly increased mortality during the first 18 days of life (43% of SS vs 14% of controls; $p<0.001$) and decreased body weights at 9 wks ($p=0.012$). In the brains, the SS effect on DNA was more pronounced in the hindbrain which contains the cerebellum and which in the rat undergoes significant postnatal development. The decrease in DNA was significant ($p=0.008$) and indicated a reduction in cell density in this region although the weights of the brain halves were not changed by SS exposure. Compared to the unexposed group, postnatal SS exposure reduced DNA in the forebrain by 2.2% ($p=0.034$) and in the hindbrain by 4.4% ($p=0.001$). This effect was accompanied by an increase in the protein/DNA ratio of 8.4% ($p=0.001$), which is taken as an indication of cell size. These data suggest that in the rat, postnatal but not prenatal SS exposure decreased brain cell numbers but increased cell size. The neurodevelopmental consequences of this change are not known nor is it clear whether these finding apply to humans. This period of postnatal neurodevelopment in the rat is thought to be equivalent to that seen during the last trimester in human fetuses. Nevertheless this study provides a plausible explanation for some of the smoke-associated neurobehavioral decrements reported in other studies.

4.1.3. Summary of SIDS Epidemiological Data

Of the additional nine studies reviewed here, all support an association between maternal postnatal smoking and SIDS with four providing adjusted odds ratios ranging from 1.43 to 5.05 (95% CIs in all cases exclude unity). Three of the four studies found an effect for paternal smoking as well (ORs 1.37-3.84), while the fourth (Dwyer *et al*., 1999) found an association between paternal smoking and cotinine levels but not SIDS. Two of the eight studies (Milerad *et al*., 1998; Rajs *et al*., 1997) examined pericardial fluid from SIDS victims and found a strong association between death by SIDS and elevated pericardial cotinine levels indicating substantial exposure to nicotine shortly prior to death. Pathophysiological changes associated with smoke exposure included thickening of the walls of the large airways in smoke-exposed, but not unexposed, SIDS victims (Elliot *et al.,* 1998). While the association between ETS and SIDS in these studies is often complicated by maternal prenatal smoking, a postnatal ETS effect is indicated by the association of paternal smoking with SIDS, and the evidence of high cotinine levels in SIDS victims relative to infants who died of other causes.

These data as well as research in animals suggest that ETS has pleiotropic effects in developing systems. In rats postnatal passive smoke exposure alters brain structure. Gospe *et al*. (1996) observed decreased cell numbers in the hindbrain, while Slotkin *et al*. (1999) found altered numbers of muscarinic and nicotinic receptors in the brainstem similar to the alterations seen in the brainstems of SIDS victims. The brainstem areas affected are involved in cardiorespiratory function, and changes in this area could potentially compromise the normal neonatal response to hypoxia. In addition, in piglets, postnatal nicotine depresses normal autoresuscitation following apnea, an effect that is exaggerated in the presence of infection (Froen *et al*., 2000).

Attributable risk

In their meta-analysis of studies controlling for prenatal smoke exposure, Anderson and Cook (1997) derived a pooled adjusted OR for SIDS associated with postnatal ETS of 1.94 (95% CI 1.55-2.43). According to the California Tobacco Control Program (CA DHS 2001), 11.4% of children 1-17 years were exposed to ETS at home. Assuming a similar exposure for neonates, and assuming, as the data suggest, that ETS has a causal role in SIDS, a population attributable risk may be calculated. Where *p* is the exposure prevalence of 11.4%, the attributable fraction (a) is given by $a = p(R-1)/(p(R-1) + 1)$ (Lilienfeld & Lilienfeld, 1980)

$$a = 0.114(1.94-1)/(0.114(1.94-1)+1) = 0.097.$$

In California in 2000 there were a reported 222 deaths due to SIDS (CA DHS, 2002). Thus in 2000 there were an estimated 21 (95% CI 13-31) excess cases of SIDS attributable to ETS exposure in California (222 * 0.097 = 21).

4.2. Cognition and Behavior

4.2.1. Summary of Previous Findings

Some evidence supportive of an association between maternal smoking during pregnancy and impaired cognitive development of the offspring was described in OEHHA's 1997 report. The evidence of an association with maternal ETS exposure was found to be limited and inconclusive. Evidence suggesting a link between postnatal ETS exposure and impaired cognition was found to be inconsistent and inconclusive.

4.2.2. New Epidemiologic Studies

With respect to behavior, assessing the effects of passive smoke exposure on outcomes as complex as human behavior is problematic at best. Bearing this in mind, two studies are presented that purport to examine the association between a child's prenatal and/or postnatal exposure to passive smoke and the subsequent development of behavior problems.

In the first study, externalizing behaviors in 5-yr olds occurred at a higher rate among the offspring of women who smoked during pregnancy and/or after childbirth than among children of nonsmoking mothers (Williams *et al*., 1998). In the prospective study by Maughan *et al*. (2001), following boys and girls from birth to age 16, the childhood onset of behavior problems was associated with both pre- and postnatal maternal smoking in a dose-dependent fashion. The highest risks were associated with heavy prenatal smoking especially when the mother continued to smoke postnatally. When the mother stopped smoking at childbirth, the risks dropped significantly, suggesting an independent postnatal effect of ETS exposure.

A recent study by Yolton *et al*. (2002) found that postnatal ETS exposure, as measured by serum cotinine, was significantly inversely correlated with cognitive development in children 6-16 years old as assessed by performance on tests of reading, math and block design.

Yolton et al., 2002. This cross-sectional study used data from NHANES III to analyze the association between serum cotinine levels and results on tests of cognitive and academic performance in 4,399 6-16 year old children. In this analysis, results on the reading and math subtests of the WRAT-R and the block and digit span subtests of the Wechsler Intelligence Scales for Children-III were compared with serum cotinine. After adjustment for gender, race, region, poverty, parent education, marital status, ferritin and blood lead, there was a significant inverse relationship between cotinine levels and scores on reading ($b = -1.07$, $p = 0.002$), math ($b = -0.76$. $p=0.01$) and block design ($b = -.23$, $p<0.001$), but not digit span ($b = -0.36$, $p = 0.36$). The authors estimated a 1-point decrement in reading scores for each 1 ng/ml increase in serum cotinine based on a standardized mean of 100. Similarly with every 5-unit increase in serum cotinine there would be a 4-point decrement in math scores based on a mean of 100, and a 1.25-point decrement in block design scores based on a standardized mean of 10. In addition, significant deficits were seen for reading ($b = -4.98$, $p = 0.01$) and block design ($b = -0.95$, $p =$

0.003) below 1 ng/ml cotinine. This study was limited in that neither the cognitive ability of the parents nor the quality of the home were assessed. These data were presented at the 2002 annual meeting of the Pediatric Academic Societies; publication is pending.

Williams et al., 1998. This was a prospective study of behavior in 5,342 5-year old children whose mothers had been recruited early in pregnancy into the Mater University of Queensland Study of Pregnancy. Information regarding social characteristics of the family and psychological characteristics of the mothers was collected at enrollment, 1 or 2 days after birth, and again at 6 months and 5 years after delivery. At each time point data were collected on the mother's smoking behavior. At the visit right after birth, this included smoking behavior during the last trimester, while at the 6 month and 5 year visits, smoking behavior for the previous 7 days was recorded. At the 5-year follow-up, mothers completed a modified Child Behavior Check List (CBCL; Achenbach & Edelbrock, 1981), and developmental, behavioral and health information was collected on the child.

Externalizing behavior problems (destructive behaviors, tantrums, mood swings, etc.) at 5 years of age, as assessed by the mothers on the CBCL, were classified progressively according to maternal smoking status before, during and after pregnancy. Never smoking mothers had the lowest rate of child behavior problems (7.9%, n=2457) compared to mothers who smoked throughout (14.7%, n=1364). Women who had never smoked until after childbirth and who were smoking at the 5-year follow up also reported increased rates of behavior problems (13.3%, n=113; p=0.04). After adjustment for smoking at other times and numerous potential confounders such as maternal age at child's birth, education, marital status, social class, parity, child's gender, employment, etc., the relative risks for externalizing behaviors associated with postnatal maternal smoking suggested a dose-dependent increase with numbers of cigarettes smoked per day: none, RR = 1; 1-9, RR = 1.65; 10-19, RR = 1.87; $\geq$ 20, RR = 1.54. Although not presented, the authors claim the 95% CIs excluded unity in all cases. After further adjustment for maternal mental health, these estimates were reduced somewhat (none, RR = 1; 1-9, RR = 1.52; 10-19, RR = 1.87; $\geq$ 20, RR = 1.29) and only the estimate for 10-19 cigarettes per day had a 95% CI reportedly excluding unity. Assuming a cause and effect relationship, the authors calculate that maternal smoking during pregnancy may account for 25% of the reported behavior

problems while maternal smoking when the child was 5 years of age may account for an additional 16%.

One of the strengths of this study is the control for a wide variety of potentially confounding and intervening variables. While this included the more commonly controlled variables of maternal and gestational ages, educational level, social class, marital status, employment, child's gender, and age at follow-up, it also included parent's country of birth and ethnicity, mother's religiosity, and number of other children. More importantly the mother's mental health was measured using the Delusion-Symptoms Status inventory in an attempt to control for the potential influence of maternal anxiety or depression on the child's behavior.

Maughan et al., 2001. The prospective 1970 British birth cohort study (BCS70) was the source of data for this study on pre- and postnatal maternal smoking and the incidence and age at onset of antisocial behavior in both male and female offspring. The study followed 2,969 boys and 2,801 girls from birth to age 16. Follow up was by questionnaire at ages 5, 10 and 16 years. Data from medical examinations, parental interviews, and cognitive tests and questionnaires completed by the children were included in the study. The study measures collected when the children were one month of age included gestational age, birth weight and maternal age, maternal smoking and drinking habits, parental education and social status, family structure and stability, and home environment. In addition, mothers and adolescents at age 16 completed the Malaise Inventory to provide an index for depression. At age 5, the children's abilities and attainments were assessed with the English Picture Vocabulary Test (EPVT). Conduct problems at ages 5 and 10 were assessed by the parents with the Rutter A2 behavior rating scales, a modified form of which was used when the children were 16.

Over 40% of the mothers smoked during pregnancy and their offspring were of lower birth weight, had significantly lower vocabulary scores at age five ($p<0.05$) and lower reading scores at age 10 ($p<0.05$). Compared with nonsmokers, and after controlling for gender, socioeconomic status, maternal age, family instability, maternal depressive symptoms, child ordinal position in family, hyperactivity, and poorer vocabulary and reading skills, logistic regression analysis showed that children whose mothers smoked 5-14 cigarettes per day prenatally had an OR for conduct problems of 1.48 (95% CI 1.18-1.85; $p=0.001$). For the heaviest smokers the adjusted

OR was 1.53 (95% CI 1.17-2.00; p=0.002). With heavy maternal prenatal smoking, conduct problems also tended to persist into adolescence with an OR of 1.69 (95% CI 1.08-2.63; p= 0.021). Among boys of heavy smokers, 30% with childhood-onset conduct problems showed persistent conduct problems by age 16 compared with 21.5% of sons of nonsmokers. Among girls of heavy smokers the persistence rate at age 16 was 29.2% versus 13.2% for girls of nonsmokers.

To determine to what extent postnatal maternal smoking contributed to the observed effects, the authors repeated the logistic regression analysis but with a 3-point cumulative index of postnatal smoking reflecting how many times (0, 1, 2) the mother reported smoking at the 5 and 10 year assessments. Controlling for the factors above, this index was significantly associated with an increased risk for conduct problems (OR 1.17; 95% CI 1.04-1.32; p=0.011). However, this effect is primarily associated with persistent smoking. That is, the adjusted OR for children of mothers who reported smoking at only one of the follow-ups was 1.20 (95% CI 0.88-1.62), not significantly different from nonsmokers' children, while for children of persistent smokers, the adjusted OR was significant at 1.37 (95% CI 1.07-1.74) with the effect becoming more pronounced as the number of cigarettes smoked increased. A weakness of this study was the estimation of smoke exposure from self-reports with no independent biochemical verification.

Overall this study supports an effect of both prenatal and postnatal smoking on the development of conduct problems. The highest risks were among children whose mothers smoked heavily during pregnancy and after. However, if the heavily smoking mother quit after pregnancy, the risk dropped to slightly above that for nonsmokers. This unexpected result suggests a significant postnatal effect of ETS exposure.

4.2.3. Conclusions

There is some suggestive evidence that both behavior and cognition are adversely affected by postnatal ETS. Due to the tendency of smoking mothers to smoke both during and after pregnancy, prenatal smoke exposure is likely to have contributed to the observed effects. However, the correlation of cognitive test scores with serum cotinine levels in children (Yolton *et al*., 2002), the observation that the risk of externalizing behaviors drops to near control levels if heavily smoking mothers stop smoking after childbirth (Maughan *et al*., 2001), and the increase in

rates of childhood conduct problems among children whose mothers start smoking after pregnancy compared with never smoking mothers (Williams *et al*., 1998), all indicate a postnatal effect of ETS.

4.3. Postnatal physical development

No new studies were found that addressed postnatal physical development in terms of altered height and weight gain. Recent studies have focused on more subtle effects of ETS on a variety of endpoints that impinge on development of specific organ systems. These include the cardiovascular system and depressed HDL-C levels, allergic sensitization in the immune system, middle ear disease which affects auditory development, elevated nucleated RBCs reflecting effects on the developing hematopoietic system, and dental caries.

4.3.1. Auditory Effects (And Secondary Neurodevelopmental effects)

Bennett & Haggard, 1998. In this study, data from a large birth cohort of 9,000 to 11,000 children in the United Kingdom were analyzed to examine the various risk factors for childhood middle ear disease (MED) including passive smoke exposure. For children in this cohort, medical and social background data were collected from the mothers by questionnaire at birth and periodically thereafter until age 21. Two markers for inner ear disease were employed: whether or not the child had suspected or confirmed hearing difficulty up to 4 years of age, and similarly for ages 4-5; and whether or not there had been any purulent ear discharge during these two time periods. Potential confounders such as non-specific ear-nose-throat (ENT) disease and the child's general health were controlled. Potential risk factors for MED such as gender, day care, length of breastfeeding, parental smoking habits, birth weight and mother's age, were treated as independent variables.

Preliminary analyses indicated little difference in the reported rates of ear discharge or hearing difficulties between the two age groups so the data for both time periods were combined. In a multiple logistic regression model controlling for social status and non-specific ENT disease, only maternal smoking was significantly associated with ear discharge with an adjusted OR of 1.28 (95% CI 1.13-1.45; $p<0.001$). The percentage of children with ear discharge also showed a dose response associated with the number of cigarettes smoked (no cigarettes, 10.5%; 1-14, 11.6%; ≥ 15, 12.1%; $p< 0.001$). After inclusion of the mother's smoking habits, none of the other

independent variables was significant. Similarly maternal smoking was associated with hearing difficulties with an OR adjusted for social index and mouth breathing/snoring of 1.31 (95% CI 1.14-1.51; $p< 0.001$). For the combined outcome of ear discharge and hearing loss, adjusted for social index and infant general health score, maternal smoking was associated with an OR of 1.60 (95% CI 1.21-2.11; $p< 0.001$). Male gender and attendance in day care were also significant risk factors for MED.

Smoking during pregnancy showed a significant dose response relationship for ear discharge at 5 years, but it was not included as a separate entry in the regression model due to the inter-relation with postnatal smoking. Mothers who smoked prenatally tended to smoke postnatally as well. However, whereas the percentage of children with both discharge and hearing loss was 2.4% for non-smoking mothers, this rate was 2.9% if the mother stopped during pregnancy, but 3.8% if she smoked 1-14 cigarettes per day ($p= 0.001$) during pregnancy and after. This suggests that ETS exposure postnatally had a deleterious effect on hearing on top of that seen from *in utero* exposure to maternal smoking. In this study, paternal smoking was not seen to have an effect. It is possible that the presence and severity of the manifestations associated with postnatal ETS reflect an interaction with conditions created by prenatal exposure, conditions which render the infant more susceptible to postnatal ETS. The significance of an ETS effect on hearing derives from observations that children with mild hearing loss associated with otitis media show deficits in higher order auditory processing (Gravel *et al.,* 1996) which in turn may cause delays in language acquisition and academic development.

4.3.2. Cardiovascular, hematological and immune effects

The role of passive smoke exposure in the development of cardiovascular disease in adults is the subject of another chapter. However children may also be at risk as suggested in the following study by Moskowitz *et al*. (1999) in which children persistently exposed to passive smoke had significantly lower serum levels of high density lipoprotein cholesterol (HDL-C), a risk factor for coronary heart disease (CHD). This effect was exacerbated if the family had a history of heart disease. Although no control for diet was evident, these results suggest a potential interaction between ETS and other risk factors for CHD in children. On the other hand, normal cardiac development in rats appears to be disrupted by prenatal nicotine exposure (Slotkin *et al*., 1999), and this effect may also apply to children and have consequences for SIDS incidence.

Moskowitz et al., 1999. Most investigations of the association between coronary heart disease (CHD) and ETS focus on adults. In this study, Moskowitz *et al*. examined how CHD risk factors, passive smoking, sex and race are related in pubertal children. Data were collected during four visits at 18-month intervals from 408 twin pairs from 11-15 years of age. Information on family and health histories, smoking, alcohol use, blood pressure, and anthropometrics was collected by questionnaire and during interview. Biochemical assays provided data on blood HDL-C, LDL-C, and cotinine. HDL-C subfraction 2 (HDL_2) was also assessed as most of the variation in HDL-C is due to this subfraction and others have shown that CHD deaths occur more frequently in families with low levels of HDL_2-C (Bodurtha *et al.,* 1987). Children with long-term passive smoke exposure had lower HDL-C than kids from nonsmoking families (visit 1: 1.21 ± 0.26 vs 1.31 ± 0.26 mmol/L; $p \leq 0.01$); similar results were observed for HDL_2 (0.31 ± 0.18 vs 0.41± 0.19 mmol/L, $p \leq 0.001$). The deleterious effects of passive smoke exposure on HDL-C levels were more pronounced in children of families with a history of cardiac disease versus those without as reflected in lower HDL-C levels (visit 1: 1.18 ± 0.23 vs 1.25 ± 0.23 mmol/mL; visit 4: 0.98 ± 0.10 vs 1.19 ± 0.18 mmol/mL; $p<0.001$). It is not clear to what extent these results are confounded by diet. Nevertheless, this study suggests that in children also, ETS exposure has a deleterious effect on HDL-C levels. Whether these effects persist into adulthood and/or increase the incidence of CHD later in life is not known.

Dollberg et al., 2000. The effects of maternal ETS exposure on absolute RBC counts were assessed in newborn infants of 55 mothers exposed and 31 not exposed to passive tobacco smoke during the last trimester. This study included only infants who were appropriate for gestational age and excluded infants of women with gestational or insulin-dependent diabetes, pregnancy-induced hypertension, placental abruption or placenta previa, any maternal heart, kidney, lung or other chronic condition, drug or alcohol abuse, perinatal infections, or infants with low Apgar scores. Complete blood counts were performed on venous blood collected within 12 hrs of birth.

There were no significant differences between exposed and unexposed groups for birth weight, gender, maternal age, gravidity or parity. However, gestational age in the smoking groups was slightly but significantly longer than in controls (< 1 week; $p=0.046$). While there were no significant differences between groups in counts for total RBCs, white blood cells, platelets or absolute lymphocytes, the counts of absolute nucleated RBCs were significantly elevated in the

passive smoke-exposed group (p = 0.02). The mean counts (range) were 357 (0-5100) for children of passive smokers versus 237 (0-1700) in controls.

Elevation of nucleated RBCs in the neonate is a marker of fetal hypoxia. The authors have previously reported elevated nucleated RBCs in infants of actively smoking mothers in which, as in this study, the hematocrit was not significantly different between exposed and control groups. Although the mechanism(s) by which smoking may cause elevated nucleated RBCs is not known, it is thought to be related to hypoxia associated with smoke-induced fetal HbCO and/or nicotine-induced placental vasoconstriction. Periods of hypoxia may stimulate bone marrow to increase the hematocrit possibly in concert with a smoke-induced more rapid RBC turnover. This study suggests that maternal passive smoke exposure has qualitatively similar effects on the fetus as active maternal smoking.

This study was relatively small. Smoking history was obtained from the mother only and not verified by biochemical measures or by other family members. On the other hand, the prospective design of this study facilitated control of potentially confounding health conditions and minimized recall bias.

Kulig et al., 1999. The incidence of allergic sensitization associated with prenatal and postnatal smoke exposure during the first three years of life was examined in this study. Sensitization was indicated by the detection of specific IgE antibodies by immunoassay. Smoke exposure was assessed by questionnaire at birth, 18 months and 3 years of age. There were four exposure categories: 178 children were not exposed; 63 were exposed only postnatally and only to the father; 28 were exposed postnatally to the mother and possibly the father; and 74 were exposed both pre- and postnatally by the mother and possibly the father. Sensitization to food, outdoor, cat or mite allergens was assumed if specific IgE antibodies were detected at least once during the first three years. Data were gathered on gender, family history of atopy, duration of breastfeeding, and parental education. Diet was not evaluated although it might be expected to have a significant effect on the development of allergies to specific foods.

After adjusting for gender, parental education and study center, and compared with children never exposed to ETS, children exposed to mother's smoking both pre- and postnatally were much more prone to developing food allergen sensitivities with an OR of 2.3 (95% CI 1.1-4.6). Postnatal

only ETS exposure from the mother was associated with an OR for food allergen sensitivity of 2.2 (95% CI 0.9-5.9). There were no significant associations between ETS exposure and sensitivity to outdoor, cat or mite allergens, nor between any allergen group and exposure to ETS from the father only. This study suggests that both prenatal maternal smoking and postnatal ETS exposures, separately or combined, have the capacity to adversely affect the developing immune system and render the child more susceptible to food allergies. That this effect was not observed for inhalant allergens may be related to the fact that allergic sensitization in infancy generally occurs first to food. Smoke exposure appears to act early in development and, in combination with food allergens, may interfere with the normal development of immunological tolerance.

4.3.3. Miscellaneous effects – Dental caries

Aligne et al., 2003. Dental records and serum cotinine levels, collected during NHANES III for 3,873 children, 4-11 years old, were used in this retrospective cross-sectional study of the association between ETS exposure and dental decay. In a logistic regression analysis adjusted for age, ethnicity, education of the household head, poverty, blood lead, time since last dental visit and geographic region, serum cotinine level was a significant predictor of caries in deciduous teeth. The adjusted OR for decayed surfaces was 1.8 (95% CI 1.2; 2.7) and 1.4 (95% CI 1.1; 2.0) for the presence of fillings. Sugar consumption and gender were not included as they were not significant factors in bivariate analyses. A significant association of ETS with dental decay was seen only for deciduous teeth but not permanent teeth. This suggests that ETS exposure has a deleterious effect on dental health that is most pronounced if it occurs early in life, perhaps during the formation of tooth enamel.

4.3.4. Animal studies of postnatal development and tobacco smoke exposure

Rumold et al. (2001) used a murine model to test whether exposure to side stream smoke (SS; a surrogate for ETS) can induce allergic sensitization to inhaled ovalbumen (OVA) in both high (BALB/c) and low (C57BL/6) IgE-responsive mice. Adult mice (6-8 wks) were exposed on 10 consecutive days to either saline or nebulized 1% OVA for 20 min., SS from 5 cigarettes for 1 hr, or SS for 1 hr followed by OVA for 20 min. Twenty days later the mice were re-exposed to 1% OVA for 20 min. Bronchoalveolar lavage (BAL) was performed 24 hours later for determination of cytokines in BAL fluid. IgE and IgG1 levels were measured in peripheral blood.

By day 18 following initiation of exposure (8 days following cessation), both total serum and OVA-specific IgE levels were significantly elevated in both high and low responders exposed to OVA/SS compared to OVA alone ($p<0.01$). Similarly IgG1 levels but not IgG2a were significantly elevated in this group ($p<0.01$). Cytokine induction (IL-5, GM-CSF, IL-2) was observed after OVA re-exposure in BAL fluid from mice exposed to SS/OVA but not in mice exposed to OVA alone. Mice exposed to SS/OVA but not OVA alone developed eosinophilia, had significantly less IFN-γ, and had increases in the Th2 cytokine IL-5. SS alone resulted in elevated GM-CSF and IL-2 upon re-exposure. The production of specific allergic antibodies to inhaled allergens is characteristic of the sensitization phase of reactive airway disease. These experiments indicate that ETS has the capacity to alter lung homeostasis and augment allergic sensitization to otherwise innocuous allergens.

4.4. Respiratory development and function

Respiratory development and function is covered in Chapter 6 (6.2.3)

4.5. Chapter Summary and Conclusions

In its examination of the association between smoke exposure and SIDS, the 1997 Cal-EPA report reached the following conclusion.

"There is adequate epidemiological evidence of a causal relationship between maternal smoking in general and risk of SIDS. In most of the studies examining the relationship between ETS exposure and SIDS, it was not possible to separate the effects of posnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent findings of elevated risk of SIDS associated with postnatal ETS exposure independent of maternal smoking in reasonably well-controlled epidemiological studies provide compelling evidence that postnatal ETS exposure of the child is an independent risk factor for SIDS."

This conclusion is substantiated by the more recent research reviewed here. While the ability to clearly separate the effects of prenatal from postnatal smoke exposure is limited in most studies, the meta-analysis by Anderson and Cook (1997) included four studies reporting postnatal effects of ETS on SIDS after controlling for prenatal maternal smoke exposure (pooled OR 1.94: 95% CI 1.55; 2.43). In addition, the finding of elevated cotinine (Milerad *et al*., 1998; Rajs *et al*., 1997)

and/or nicotine (McMartin *et al*., 2002) in tissues of infants who died from SIDS compared to non-SIDS deaths supports a postnatal effect of ETS. It could be argued that these levels merely reflect a continuation of smoke exposure that started prior to birth. However, the observation by Alm *et al*. (1998) that cessation of maternal smoking at parturition is associated with a dramatic drop in the risk of SIDS compared to that seen with continued smoking argues for a postnatal ETS effect. So too do the studies that find increased risks for SIDS associated with paternal smoking (Brooke *et al*., 1997; Mitchell *et al*., 1997).

The association of ETS with SIDS is further strengthened by the delineation of several probable mechanisms based on tobacco-related changes in the brainstem regions controlling cardio-respiratory responses, the muscarinic and adrenergic receptors in the heart, and thickening of the airways in the lungs. Infants exposed to tobacco smoke also tend to have inflamed airways and are at higher risk of developing allergies and pulmonary infections. These conditions in combination with an infant's ETS-compromised ability to resuscitate in response to smoke or apnea-induced hypoxia significantly increase the chances of SIDS occurring in ETS-exposed infants. Indeed we estimate that in California in 2000, despite the low exposure of infants to secondhand smoke compared to the rest of the country, approximately 10% of the SIDS deaths (21/222) were attributable to ETS.

With respect to neurobehavioral effects, there is epidemiological evidence suggesting that maternal smoking during pregnancy has deleterious effects on neurodevelopment. However, the role of postnatal ETS exposure in cognitive development has been less extensively studied and, as a result, it is not clear to what extent ETS exposure may directly modify a child's cognitive development. On the other hand, behavioral outcomes as manifested in childhood conduct problems appear to be negatively influenced by ETS exposure. The studies in this area are limited in number but suggest that pre- and/or postnatal passive smoke exposures may increase the risk for conduct disorders in the children so exposed.

ETS exposure has negative effects on diverse systems and exacerbates underlying conditions. Its effects on the immune system increase the development of allergies in exposed children. ETS-associated decreases in HDL-C in children may predispose to the subsequent development of heart disease, while the increase in middle ear disease associated with ETS influences auditory

and neural development. The risks associated with each of these effects individually may be cumulative and the large and diverse number of effects increases the likelihood that ETS exposure will have a significant negative impact on exposed individuals.

4.6. References

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